REMARKS

Claims 28-32 are pending in this application. Claim 28 has been amended, and Claims 31 and 32 have been withdrawn by the Examiner. As such, Claims 28-30 were considered on the merits. The Examiner issued a single obviousness rejection, which is discussed below.

I. Obviousness Rejection over Hirsch et al. in view of Robinson et al.

The Examiner rejected claims 28-30 under 35 U.S.C. 103(a) as allegedly obvious over Hirsch et al. in view of Robinson et al. In particular, the Examiner cites Hirsch et al. as teaching the combined use of AZT (zidovudine) with other agents, such as protease inhibitors. The Examiner also cites Hirsch et al. for teaching that patients can become resistant to AZT, and for providing a reference to hypothetical integrase inhibitors in Table 1. The Examiner alleges that it would have been obvious to combine the integrase inhibitors of Robinson et al. with Hirsch et al. since Hirsch et al. discusses combination therapy with AZT. Applicants respectfully disagree with this rejection.

A. The Claims Specify Administration of the SAME Reverse Transcriptase Inhibitor to which the Patient is At Least Partially Resistant

One important aspect of the current claims is the fact that the patient is administered the same reverse transcriptase inhibitor to which they are at least partially resistant. In other words, the claims are not simply to administering ANY combination of a reverse transcriptase inhibitor and an integrase inhibitor, but instead specifically recite that the patient be administered the very same reverse transcriptase inhibitor to which they have become at least partially resistant. The patient in the claims, therefore, is given a reverse transcriptase inhibitor that should not work very well (or at all) to treat the HIV virus in the patient.

A review of the Examiner's rejection makes it appear that the claims have been read to cover the administration of ANY combination of a reverse transcriptase inhibitor and an integrase inhibitor, rather than requiring that the reverse transcriptase be one for which the patient is at least partially resistant. For example, the Examiner states "[i]t is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose." (Office Action, page 4). The reverse transcriptase in the claims, however, if administered alone would NOT have the same utility as the integrase inhibitor (administered

alone) because the claims specify that the *patient be at least partially resistant to the particular reverse transcriptase inhibitor.* As such, it would appear that the Examiner has not considered all of the limitations of the claims in issuing the obviousness rejection.

The fact that the claims recite that the reverse transcriptase administered is the same reverse transcriptase that the patient is at least partially resistant to is important as it highlights the lack of obviousness of the claims. For example, if a patient were resistant or partially resistant to a particular reverse transcriptase inhibitor, such as AZT, why would the patient nonetheless still receive the reverse transcriptase inhibitor (in combination with an integrase inhibitor) as opposed to a different reverse transcriptase inhibitor to which the patient is not yet resistant? Particularly when there were numerous reverse transcriptase inhibitors known in the art prior to the priority date of the present invention. This question is particularly relevant to the present claims as the art has reported that "continued treatment in the face of AZT resistance may be like no treatment at all." (see, Japour at Tab A). In light of this, Applicants submit the present invention would not be obvious to one of skill in the art.

The primary reference cited by the Examiner, Hirsch et al., further highlights the fact that it would not be obvious to one of skill in the art to treat a patient with a reverse transcriptase to which the patient is at least partially resistant. For example, even ignoring the cost associated with administering a reverse transcriptase inhibitor that may "be like no treatment at all," Hirsch et al. reports a number of side effects of AZT including anemia, leukopenia, and myopathy characterized by inhibition of mitochondrial DNA replication and elevated serum creatine kinase concentrations (see, Hirsch et al., page 1688, 1st column). Subjecting a patient to the risks of side effects, for no perceived benefit, is not logical and is counter to how modern medicine is practiced. As such, this again highlights the lack of obviousness of the present claims that nonetheless call for the reverse transcriptase inhibitor to be administered to a patient that is at least partially resistant. Therefore, Applicants submit that this rejection should be withdrawn.

B. Claim Amendment Specifying a Synergistic Therapeutic Effect

In light of the above, it is clear that the prior art cited by the Examiner does not render the claims obvious. Nonetheless, in order to expedite the allowance of the present application, without acquiescing to the Examiner's rejection, while reserving the right to prosecute the original claims in the future, Applicants have amended the claims. In particular, Claim 28 has been amended to recite that:

> the combination of said reverse transcriptase inhibitor and said integrase inhibitor produce a synergistic therapeutic effect on said patient that is greater than the sum of the effect observed if said transcriptase inhibitor and said integrase inhibitor were administered individually.

This amendment, reciting a synergistic effect between the reverse transcriptase and integrase inhibitors, is supported in the specification, including, for example: page 19, line 16 - page 23, line 6; Figure 5; Table 3, Table 4, and Table 6.

This amendment highlights the unexpected results provided by the claimed invention. In particular, it is unexpected that an integrase inhibitor would be able to 'reinvigorate' a reverse transcriptase inhibitor in a patient that had become at least partially resistant to such reverse transcriptase inhibitor such that a synergistic therapeutic effect is observed. It is noted that this is not simply a case where two compounds known to work for a particular patient type are shown to have a synergistic effect (as opposed to a neutral or antagonistic effect). Instead, the claimed invention is where there is a combination of one compound known to work and another that should not work (or work only poorly) and yet, not only is an additive effect produced, but more than that, a synergist effect is produced (see, Table 3).

A simple mathematical analogy further demonstrates the unexpected nature of the present invention. If one were combining two compounds both known to treat AIDS (as in the Hirsch et al. reference), and these compounds were designated as "3s," the additive effect these compounds would produce could be represented at 3 + 3 = 6, where the synergistic effect could be represented as 3 x 3 = 9. In the present case, where one of the compounds (reverse transcriptase inhibitor) was known to only work poorly (or not at all) since the patient was at least partially resistant, the mathematical analogy could be depicted as follows. The integrase inhibitor could be designated as a "3," and the reverse transcriptase inhibitor could be designated as a "1" or even a "0" (since it may have little or no effect on the reverse transcriptase inhibitor resistant patient), then the surprising synergistic effect could be depicted as, for example, 3 x 0 = 7, or 3 x 1 = 8. This type of unexpected reinvigorating effect on the reverse transcriptase inhibitor highlights the lack of obviousness of the presently amended claims.

The lack of obviousness of the present claims is particularly clear as no reference has been cited that indicates that integrase inhibitors can have this reinvigorating effect when combined with a reverse transcriptase inhibitor when administered to a patient that is at least partially resistant to that particular reverse transcriptase inhibitor. Without resorting to impermissible

hindsight reconstruction, one of skill in the art would not have expected integrase inhibitors to have such a unexpected therapeutic effect. As such, Applicants submit that the amended claims are not obvious and this rejection should be withdrawn and the claims allowed.

CONCLUSION

Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned at 608-218-6900.

Dated: November 13, 2007

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TAB A

Japour, *AIDS Clin. Care.,* 1995 Aug;7(8):63-5, 67.

AIDS CLINICAL CARE

FEATURE TOPIC

Antiretroviral Drug Resistance

Clinical Significance and Implications for HIV Pathogenesis

The study of HIV-1 drug resistance has proven to be a powerful tool for advancing our knowledge of the basic pathogenetic mechanisms of HIV disease. Two articles published this year by Wei and coworkers[1] and Ho and coworkers[2] exploited the emergence of drug-resistant variants to explore the kinetics of virus production and clearance in patients. While chronic persistent viral replication over time is the centerpiece of HIV disease pathogenesis, relatively little has been known about the natural history of HIV viral dynamics in humans. The two research teams' findings were virtually identical. Notably, clinicians and virologists worked closely with mathematicians and statisticians to produce a model of virus turnover. Intensive virologic monitoring of plasma HIV-1 RNA levels in patients receiving two experimental drugs revealed that while these highly potent drugs reduced viral load by 99.9%, the effects were transient because of the rapid emergence of drug-resistance-conferring mutations in the protease and reverse transcriptase genes.

At face value, it may appear that the clinical use of these drugs is limited (at least as monotherapy). The silver lining in this disappointing outcome in the clinical trial, however, was that the rapid emergence of drug resistance proved to be key to understanding virus turnover. Four weeks of treatment with the antiretroviral agents led to up to 2 logs of plasma HIV-1 RNA decline with corresponding increases in CD4+ cell counts. After four weeks of treatment, viral load rebounded, and CD4+ cell counts fell to pretreatment levels while the virus population turned over from exclusively wild type virus to drug-resistant variants. By analyzing the appearance of resistant HIV in patients' plasma, investigators estimated the HIV elimination half-life to be approximately two days. It appears that, among patients with less than 500 CD4+ cells, approximately one billion virions (roughly 33% of the total viral load) are being produced and cleared daily. Roughly the same number of CD4+ cells (about 1% of the total) are produced and destroyed each day. After examining the mutations in peripheral blood mononuclear cells (PBMC), it was found that their half-life was 50-100 days. The dissociation between the timing in the appearance of drug-resistant mutants in plasma and in PBMC further supports the notion that other cell populations (such as in the lymph nodes and other lymphoreticular organs) are largely responsible for the circulating virus load. That is, if mutations are found in plasma before they appear in circulating PBMCs, then, to use a plumbing analogy, the plasma is to reticuloendothelial organs as the water is to the dishwasher.

AZT *resistance is associated with more rapid progression of disease.*

For the most part, the international scientific community agrees with the findings of Ho et al. and Wei et al. Controversy remains, however, about the reason for the changes in CD4+ cell count following initiation of antiviral therapy. The investigators concluded that the changes are related to clearance of CD4+ cells as a function

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Deborah J. Cotton, MD, MPH

CASE WATCH

from the Centers for Disease Control and the World Health Organization

WORLD AIDS CASES	**4,500,000***
U.S. AIDS CASES	**461,234†**
U.S. AIDS DEATHS	**282,220†**

*Estimated
†Reported through 4/25/95 by CDC

Founded in cooperation with American Foundation for AIDS Research

of time. Other scientists have proposed alternative explanations, such as that therapy triggers a mobilization of CD4+ cells from infected lymphoid tissue. Still others suggest that the CD4+ cell increase may be an epiphenomenon in which a decreased viral load results in a reduction in the number of CD4+ cells trapped in the lymphoreticular organs.[3]

While the clinical significance of viral dynamics is apparent, it remains unclear to what extent these data can be applied in the clinical setting. Some authorities have interpreted these findings to suggest that since viral replication occurs 24 hours a day, patients should be treated at all stages of disease. Further, it has been suggested that combination treatments are the only hope. The other side of the debate points out that there is not an inexhaustible number of available drugs that allows the clinician to swiftly move from one combination to another at monthly intervals as the viral population shifts from sensitive to mutant. Secondly, continuous treatment with periodic modest decreases in viral load may not translate into long-term clinical benefit.

AZT resistance

AZT was approved by the U.S. Food and Drug Administration (FDA) in 1987. In 1989, AZT-resistant HIV-1 was first reported among HIV-1-positive individuals treated with extended courses of AZT. In vitro assays showed one-to-two log reductions in HIV-1 susceptibility to AZT among HIV-1 isolates taken from AZT-treated patients. Several studies have now shown that the clinical benefit of AZT monotherapy is limited. The mechanism for this clinical finding has been difficult to establish, due initially to methodologic issues related to the detection of antiretroviral drug resistance. Virological and molecular biological techniques have now been developed that can be used to explore the relation between resistance and clinical outcome.

Virologists at five ACTG centers analyzed the HIV isolates stored from a subset of individuals who had participated in a randomized, controlled trial (ACTG 116B/117)[4,5] comparing the efficacy of continued AZT versus a switch to ddI in patients who had been previously treated with AZT for at least four months. The finding of the clinical trial, which followed patients for an average of approximately one year, was that changing treatment to ddI appeared to slow the progression of HIV disease.

In both studies, AZT resistance (as determined by either a direct susceptibility assay or the presence of reverse transcriptase resistance-conferring mutations) at study entry was associated with more rapid clinical progression and death. While other retrospective studies had found a similar association, they had not controlled for other clinical and virologic factors that are also associated with poor outcome. The 116B/117 resistance studies controlled for baseline CD4+ cell count, a diagnosis of AIDS at study entry, treatment assignment, and the presence of syncytium-inducing phenotype. When these variables were controlled in multiple regression models, the risk of increased progression with AZT resistance remained strongly significant (relative hazard, 1.82; 95% confidence interval, 1.02-3.260).

Continued treatment in the face of AZT resistance may be like no treatment at all.

Another striking feature of the results of ACTG 116B/117 was that using death as the clinical endpoint, the relative risk of death among patients with AZT-resistant HIV was three- to five-fold higher than for patients with AZT-susceptible HIV isolates, (rh 5.42; 95% CI, 1.92-15.30). This very high risk of death associated with AZT resistance is not well explained. Moreover, patients with AZT resistance who were switched to ddI apparently had no greater benefit from the switch in treatment to ddI than did patients with AZT-sensitive virus. It is worth noting here that the virologic study did not have sufficient statistical power to fully estimate differences within each treatment arm. It may well be that AZT-resistant HIV is a marker for poor immunologic function incompletely represented by CD4+ cell counts or viral load. It is also possible that AZT-resistant viruses are more highly pathogenic strains of HIV. In summary, while previous work provided seminal information on the existence of HIV drug resistance, these studies confirm the association of AZT resistance with more rapid progression of HIV disease and earlier death.

John Coffin has proposed a model for shifts in viral quasi-species (viral variants that are subtly different from others in the HIV population) that may account for the emergence of either more pathogenic virus strains or strains that replicate more vigorously in the setting of antiretroviral treatment.[6] In this model, the assumption is that all possible mutations are present de novo and that the replicating populations of virus are exquisitely sensitive to exogenous pressures to decrease virus load. While these mutations exist, they must not replicate as well as the wild type virus, otherwise they would comprise the wild type, or most "fit," population. Therefore, as Dr. Coffin suggests, a Darwinian situation — "survival of the fittest" — is established. HIV populations compete with each other, while subtle mutations in the reverse transcriptase gene affect the replicative capacity of that variant positively or negatively, and ultimately determine the varient's viability. While the emergence of the mutant population can occur due to the propensity of the HIV reverse transcriptase enzyme to misincorporate nucleotides during replication, a positive selective advantage rendered by a more fit virus is likely to have a greater impact on the surviving mutants.

Analysis of HIV strains following the withdrawal of AZT treatment show that AZT-resistant populations are still actively replicating in the absence of selective AZT pressure; that is, the wild type does not supplant the AZT-resistant HIV species after discontinuation of AZT therapy.[7] This finding suggests that AZT-resistant viruses are quite "fit," and while they may not have arisen without the pressure of AZT treatment, once established, they will become the dominant circulating quasi-species, perhaps indefinitely. Therefore, continued treatment in the face of AZT resistance may be like no treatment at all.

ddI, ddC, d4T and 3TC resistance

The clinical significance of resistance to the dideoxynucleoside agents (ddI, ddC, d4T and 3TC) remains incompletely understood. When ddI is used as monotherapy, a mutation (codon 74 leu → val) conferring a 6- to 10-fold decrease in susceptibility has been noted to occur as early as eight weeks into therapy. Kozal and coworkers conducted a retrospective study analyzing HIV isolates from patients who were switched to ddI after previous treatment with AZT.[8] The development of the ddI resistance mutation was associated with a decrease in CD4+ cell counts. After 24 weeks of treatment, patients who developed the mutation also had higher mean HIV RNA copies/mL.

ddC resistance has been found to occur after treatment of patients with ddC monotherapy. Of clinical interest is that, in patients enrolled in a ddC study, two ddC resistance-conferring mutations (65 lys → arg and 184 met → val) were cross-resistant to 3TC and ddI.[9] While the clinical significance of these observations remains uncertain, the findings indicate that ddC-treated patients who develop these mutations may not benefit from a switch to ddI or 3TC.

Resistance to d4T, the antiretroviral agent most recently approved by the FDA, was selected in vitro by serial passage of HIV through a culture containing d4T. A mutation (75 val → thr) in the reverse transcriptase gene has been found to be associated with a modest decrease in d4T susceptibility with cross-resistance to ddI and ddC.[10] However, when Lin and coworkers analyzed HIV isolates from patients treated with long-term d4T monotherapy, only 1 of 13 patients was found to carry the codon 75 mutation, and the same patient's isolate was not found to be d4T-resistant.[11] Moreover, nearly half the patients in this d4T trial developed AZT resistance. It is possible that patients were taking AZT outside the study but, unfortunately, d4T, like AZT, raises mean corpuscular volume; the investigators were therefore unable to determine easily whether study participants were taking AZT simultaneously. If patients were surreptitiously taking AZT as well as d4T, the d4T-resistant mutant virus may have been suppressed in favor of the more replication-competent AZT-resistant strain.

3TC monotherapy results in the development of high level 3TC resistance in a matter of weeks; this is conferred by a mutation (codon 184 met → val). HIV RNA load rebounds after an initial decrease that is temporally associated with the appearance of these mutants.[12] The 184 met → val mutant is cross-resistant to ddI and ddC.

Combination therapies and multidrug resistance

Despite the widespread clinical practice of using combination treatment regimens, no study has proven that combination therapy delays HIV disease progression or death over the long term. For symptomatic patients with CD4+ counts under 300/mm^3 or asymptomatic patients with CD4+ counts under 200 who had been previously treated with AZT for at least six months, ACTG 155 showed no overall benefit for combining AZT with ddC over switching to ddC alone or even to continuing AZT alone.[13]

These ACTG 155 findings are in sharp contrast to expectations, given the results of two other large phase III trials by Kahn and coworkers (ACTG 116B/ 117) and Abrams and coworkers (CPCRA 002).[14,15] All three studies enrolled patients whose median previous AZT treatment was 13 to 18 months. If ddI is superior to AZT in this setting (which were the findings of Kahn and coworkers) and ddC is equivalent to or possibly better than ddI (according to the findings of Abrams and coworkers), then why was a switch to ddC in ACTG 155 not better than continued AZT?

Substudy analysis suggested that combination treatment might have been of benefit among patients with higher CD4+ counts. However, the overall study population in ACTG 155 had significantly higher CD4+ (median 127) counts at entry than patients in either ACTG 116B/117 (median 97) or the CPCRA study (median 75). The mixed conclusions of the clinical trials reflect the limitations of our understanding of the pathogenesis of HIV disease at the time they were initiated, as well as, perhaps, changes in standards of care for prophylaxis and treatment of opportunistic infections.

Multidrug regimens are being assessed that combine antiretroviral agents in two, three, or more drug regimens as a means of preventing or delaying the emergence of AZT-resistant strains of HIV. Virologic analysis of two phase II studies of AZT plus ddI have shown that mutations conferring AZT resistance occurred as readily in

(Continued on page 67)

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(Continued from page 65)

the combination arm as in the AZT monotherapy arm.[16,17] Interestingly, while the emergence of AZT-resistant virus was not affected by the addition of ddI (in simultaneous or alternating regimens), the emergence of the ddI resistance-conferring mutation (codon 74 leu → val) was blocked with the combination regimen. Similarly, the combination of AZT and ddC did not delay the emergence of AZT resistance, but ddC resistance did not develop.[17] Preliminary studies suggest that 3TC treatment and the M184V mutation may prevent the emergence of AZT-resistant virus.

It seems possible, then, that by using two drugs (say drug X and drug Y), a sustained treatment benefit might be achieved if drug X prevents the emergence of resistance to Y despite the development of resistance to X. Therefore, in the absence of an ability to completely shut off viral replication, the goal of combination treatments might be to select for a resistant but crippled mutant. If the convergent combination theory relies on evolutionary limitations to prevent the emergence of multidrug resistance by impairing HIV replication, then, by contrast, the model described above would selectively induce a shift toward a drug-resistant quasi-species that is replication-competent, but less so than the wild type or alternative mutant strains. This is an attractive theory, but it is tempered by findings of a unique pattern of mutations that confer resistance to both AZT and ddI among some individuals treated with the combination of AZT and ddI.[18,19]

The potential clinical use of nonnucleoside reverse transcriptase inhibitors appears to be limited to combination strategies. Resistance to these drugs emerges as early as one week[20]; coincident with the development of resistance, viral load rebounds and CD4+ cell count falls. Nevirapine monotherapy resulted in several mutations conferring high-level resistance, the most common of which was the codon 181 tyr → cys mutant. When AZT was added to nevirapine in a combination regimen, viruses with the 181 mutation were blocked; however, strains with other mutations readily arose. Nevirapine resistance occurred whether nevirapine and AZT were given in an alternating or simultaneous regimen.[21] Three combination drug regimens that include AZT, ddI, and nevirapine are under investigation, but in vitro studies have shown that triply-resistant viruses can be selected and are viable.[22]

Public health considerations

A discussion of the clinical significance of HIV drug resistance would not be complete without mention of the public health consequences of the widespread clinical use of antiretroviral agents. Human-to-human transmission of AZT-resistant HIV has been documented, including one case of apparent sexual transmission that was published by Erice and coworkers.[23] Careful monitoring of newly acquired HIV by the Walter Reed Army Institute has uncovered an insidious increase in seroconversion with AZT-resistant HIV: from less than 3% in the 1988 to 1990 period, to 8% in 1992, to 15% in the 1993 to 1994 time frame, as reported by Mayers and coworkers.[24] Frenkel and coworkers have reported a case of perinatal transmission of AZT-resistant HIV.[25]

In summary, none of the current FDA-approved drugs for HIV disease — either alone or in combination — have proved to have long-term, sustained antiviral efficacy. HIV RNA as a quantitative marker of in vivo viral replication now allows greater precision in understanding the interplay between viral load and drug resistance. The pattern that is emerging is that all antiretroviral regimens — whether monotherapy or combination therapy — lead to an initial decline in viral load that is followed by a viral rebound and concurrent emergence of drug-resistant mutants. In fact, it appears that the more potent the drug, the more rapidly the resistant mutants emerge. In the future, more emphasis should be placed on incorporating resistance testing into prospective studies. Assessing efficacy for individual patients will ultimately require intensive virologic monitoring. The time is right for a paradigm shift in HIV clinical studies. ■

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